REMARKS

A check for the fee for a three-month extension of time accompanies this response. Any fees that may be due in connection with filing this paper or with this application may be charged to Deposit Account No. 50-1213. If a Petition for Extension of time is needed, this paper is to be considered such Petition.

Claims 1-75 are pending in this application. Claim 3 is amended to correct a minor typographical error. The specification is amended to correct minor typographical and grammatical errors. No new matter is added. A marked-up copy showing changes made to the specification and to claim 3, pursuant to 37 C.F.R. §1.121, is attached hereto.

INFORMATION DISCLOSURE STATEMENT

In our review of the PTO PAIR File Contents History, we find that the original Information Disclosure Statement (IDS), containing five volumes of references and a twenty-seven page PTO-1449 form, which was hand-delivered on November 5, 2001, was not entered into the PAIR system. Please find attached for your reference a copy of the IDS and the PTO-1449 forms and a stamped return postcard. A supplemental IDS submitted on June 5, 2002, has been entered into the PAIR system. Please verify that the original IDS and accompanying references hand-delivered November 5, 2001, were received. Return of the initialed forms PTO-1449 is respectfully requested.

TRAVERSAL OF RESTRICTION REQUIREMENT

Claims 1-75 are presently pending and are subject to a Restriction Requirement. The Office Action sets forth twenty-six (26) groups for election. Applicant respectfully traverses the restriction requirement.

Summary

Applicant traverses the requirement for restriction on the following bases. The subject matter of the claims is directed to a single gene, the human AKAP10 gene, and its allelic variants, and primers, kits, and methods using each allele or portion thereof. The allelic variants are single nucleotide polymorphisms

associated with the human AKAP10 gene. Thus, the instant application is directed to allelic variations of the same protein. As discussed in more detail below, MPEP §803.04 states that nucleotide sequences encoding the same protein are not considered to be independent and distinct inventions. Therefore, because the instant application claims subject matter directed to allelic variations of the same protein, the restriction requirement is improper, in so far as it restricts the alleles. Applicant further submits that the Restriction Requirement improperly restricts the claimed subject matter to a single nucleotide sequence per claim.

Applicant also respectfully submits that the Restriction Requirement as currently drafted contains errors. For example, applicant respectfully submits that some of the claims have been put in the wrong groups, and groups related as combination/subcombination are improperly restricted, as described in detail below. Finally, if the restriction requirement is maintained, Applicant respectfully submits that the applicant ultimately could be granted multiple patents that expire on different dates, each of which would include claims to overlapping subject matter, where the later issuing patents could not be held to constitute obviousness-type double patenting.

Claimed Subject Matter is Directed to SNPs of One Gene

It is respectfully submitted that the Restriction Requirement as drafted, which separates the claimed subject matter by each claimed polymorphism of the AKAP10 gene, is improper. In order for restriction to be proper, under 37 C.F.R. §§1.141 and 1.142, the restricted subject matter must be independent or distinct, and there must be a burden on the Office to examine the claims in the same application. It is respectfully submitted that in this instance, the claimed "inventions" are not independent and distinct.

Subject Matter Is Not Independent or Distinct

All of the claims in the pending application are based upon applicant's discovery of single nucleotide polymorphisms (SNPs) associated with the human

AKAP10 gene. The claimed subject matter is patentable on that basis (although other bases for patentability exist). MPEP §803.04 states:

> [N]ucleotide sequences encoding the same protein are not considered to be independent and distinct inventions and will continue to be examined together.

The instantly claimed SNPs are allelic variations of a single gene, the human AKAP10 gene, which encodes the same protein, the human AKAP10 protein. Thus, because the claimed SNPs are allelic variations of a single gene encoding the same protein, they are not considered to be independent and distinct inventions. In order for restriction to be proper, under 37 C.F.R. §§1.141 and 1.142, the restricted subject matter must be independent or distinct. Therefore, because the instantly claimed allelic variations of a single gene encoding the same protein are not considered independent and distinct inventions, restriction is improper.

Restrictions to Single Nucleotide Sequences

Restrictions to single nucleotide sequences are discussed in §803.04 of the Manual of Patent Examining Procedure (MPEP). According to MPEP §803.04, claims drawn to nucleotide sequences encoding different proteins are deemed properly restrictable, although the Commissioner has decided *sua sponte* to partially waive this requirement for a reasonable number (usually, ten) of patentably distinct sequences. MPEP §803.04 states:

> Accordingly, in most cases, up to ten independent and distinct nucleotide sequences will be examined in a single application without restriction. In addition to the specifically selected sequences, those sequences which are patently indistinct from the selected sequences will also be examined. Furthermore, nucleotide sequences encoding the same protein are not considered to be independent and distinct inventions and will continue to be examined together.

Thus, the restriction requirement among groups IV-VI, VII-IX, XIII-XV, XVI-XVIII, XIX-XXII, and XXIII-XXVI as set forth is not proper. For example, the requirement as set forth restricts the claims in Groups IV-VI to a single

nucleotide sequence. Groups IV-VI include claims 38-43, directed to a method for indicating susceptibility to morbidity including detecting the presence or absence of an allelic variant of a polymorphic region of a human AKAP10 gene. Claims 39 and 43 recite:

> 39. (Amended) The method of claim 38, wherein a polymorphic region of the AKAP10 gene comprises a nucleotide other than an A at a position corresponding to position 2073 of the coding sequence of the AKAP10 gene or other than a T of the complement of the coding sequence of the AKAP10 gene.
>
> 43. The method of claim 39, further comprising:
> detecting an allelic variant at another polymorphic region of an AKAP10 gene selected from the group consisting of a position corresponding to position 83,587 of SEQ ID NO: 13, a position corresponding to position 129,600 of SEQ ID NO: 14 and a position corresponding to position 156,277 of SEQ ID NO: 18.

The Office restricts the claimed subject matter into three groups, based on the sequences listed in claim 43. Group IV is restricted to the method where the allelic variant at another polymorphic region corresponds to position 83,587 of SEQ ID NO: 13. Group V is restricted to the method where the allelic variant corresponds to position 129,600 of SEQ ID NO: 14. Group VI is restricted to the method where the variant corresponds to position 156,277 of SEQ ID NO: 18.

As discussed above, MPEP §803.04 states that, in most cases, up to ten independent and distinct nucleotide sequences will be examined in a single application without restriction, and that nucleotide sequences encoding the same protein are not considered to be independent and distinct inventions and will be examined together. It is respectfully submitted that the claimed nucleotide sequences represent different alleles of the same gene encoding the same protein. For example, within related Groups IV-VI, the claims are directed to an allelic variant of an AKAP10 gene, and the claimed sequences are directed to the nucleotide sequence of chromosome 17 containing the genomic sequence of the AKAP10 gene or one of its allelic variants. SEQ ID NO. 13 is the nucleotide sequence of the single nucleotide polymorphism allelic variant AKAP10-6. SEQ ID NO. 14 is the nucleotide sequence of the a single

nucleotide polymorphism allelic variant AKAP10-7. SEQ ID NO. 18 is the nucleotide sequence of the single nucleotide polymorphism allelic variant AKAP10-1.

Thus, SEQ ID NOS. 13, 14 and 18 are sequences of the human AKAP10 gene on chromosome 17, and represent a single nucleotide polymorphism allelic variant thereof. Hence, these nucleotide sequences represent different alleles of the same gene encoding the same protein. A search of the human AKAP10 gene will be required for all sequences, and thus there is no undue burden on the Office. Therefore, the restriction between Groups IV-VI is improper.

Similarly, within related Groups VII-IX, there are only six nucleic acid or protein sequences, SEQ ID NOS. 1, 3, 13, 14, 17, and 18. SEQ ID NOS. 13, 14, and 18 are discussed immediately above, and are directed to the AKAP10 gene or one of its allelic variants. Similarly, SEQ ID NO.1 is the nucleotide sequence of the wild type AKAP10 gene, and SEQ ID NO. 17 is the sequence of chromosome 17 containing the genomic sequence of the predominate allele of the AKAP10 gene. SEQ ID NO. 3 is the nucleotide sequence of chromosome 17 containing the genomic sequence of the allelic variant AKAP10-5, which is a single nucleotide polymorphism at position 2073 of the AKAP10 gene. Hence, SEQ ID NOS. 1, 3, 13, 14, 17, and 18 are sequences of the human AKAP10 gene on chromosome 17, and represent the wild type or an SNP allelic variant thereof. Hence, these nucleotide sequences represent different alleles of the same gene. The same search is clearly required for all of the sequences. Therefore, the restriction between Groups VII-IX is improper.

The same argument can be made for the restriction between Groups XIII-XV, Groups XVI-XVIII, and Groups XIX-XXII, which have been restricted to one of SEQ ID NOS. 1, 3, 13, 14, and 18, all of which represent different alleles of the same gene. The same search is clearly required for all of the sequences. Therefore, the restriction of Groups XIII-XV, Groups XVI-XVIII, and Groups XIX-XXII is improper.

Finally, the subject matter of claim 75 is currently restricted to Groups XXIII through XXVI. Claim 75 is directed to primers including the nucleotide sequence of SEQ ID NOS. 8, 15, 19, and 20. The Office restricts the claimed subject matter into four distinct groups, based on these sequences. MPEP §803.04 states that in most cases, up to ten independent and distinct nucleotide sequences will be examined in a single application without restriction. Within Groups XXIII through XXVI, the claims are directed to primers including the nucleotide sequence corresponding to SEQ ID NOS. 8, 15, 19, or 20. Thus, these sets of claims are directed to no more than four sequences. Applicant respectfully submits that, because there are fewer than ten sequences claimed within claim 75, the restriction between Groups XXIII-XXVI is improper.

THE RESTRICTION REQUIREMENT SHOULD BE REDRAFTED

If the Restriction Requirement is maintained, applicant respectfully submits that the restriction requirement should be redrafted. As currently drafted, the Restriction Requirement incorrectly restricts claims from appropriate groups, and improperly restricts claims directed to subject matter that is related as combination/subcombination.

Incorrect Restriction

Claims 9 and 10

Applicant respectfully submits that claims 9 and 10 are incorrectly restricted from group I. Claims 9 and 10 are directed to a portion of the polypeptide encoded by the nucleic acid molecule of claim 1. Thus, the subject matter of claims 9 and 10 is a composition of matter. In the Requirement for Restriction as presently drafted, Claims 9 and 10 are restricted to Group X, which is directed to a method for growing a host cell. Claims 9 and 10 are not directed to a method for growing a host cell, but instead are directed to a portion of the polypeptide encoded by the nucleic acid molecule of claim 1. Claims 9 and 10 have the same essential steps as set forth in claim 1: ascertaining the sequence of a nucleic acid molecule of the AKAP10 gene

including a sequence of nucleotides that encodes the polypeptide set forth as SEQ ID No. 2 where the Ile residue at position 646 is replaced. Claim 1 has been restricted to Group I, which is directed to subject matter including an isolated nucleic acid molecule including a sequence of nucleotides that encodes the polypeptide set forth as SEQ ID NO. 2. Thus, claims 9 and 10 present subject matter that should be included in Group I, as the Restriction Requirement is currently drawn.

Claims 32-37

Applicant respectfully submits that claims 32-37 are incorrectly restricted from group II. Group II (claims 21-31) and Group III (claims 21 and 32-37) are directed to a method for detecting the presence or absence of an allelic variant of a human AKAP10 gene. The Examiner contends that Group II is restrictable from Group III because Group II includes the method step of determining the identity of the nucleotide at a position adjacent to a position corresponding to position 2073 of SEQ ID No. 1, while Group III includes the method step of determining the identity of the nucleotide at a position corresponding to a position corresponding to position 2073 of SEQ ID No. 1. Applicant respectfully submits that the Examiner is mistaken. Claim 21, from which claims 22-37 depend, recites:

> 21. A method for detecting the presence or absence of an allelic variant of a human AKAP10 gene, comprising determining the identity of the nucleotide at a position corresponding to position 2073 of the coding sequence of a human AKAP10 gene or the complement thereof, wherein a variant has a nucleotide other than A at a position corresponding to position 2073.

The recitation "adjacent" occurs only once in claims 21-37, specifically in claim 22, in which the recitation "adjacent" refers to the hybridization of a primer to a target nucleic acid:

> 22. The method of claim 21, wherein determining the identity comprises:
> (a) hybridizing a target nucleic acid comprising a human AKAP10-encoding nucleic acid or fragment thereof or a complement of a

human AKAP10-encoding nucleic acid or fragment thereof with a nucleic acid primer that hybridizes adjacent to a position corresponding to position 2073 of the coding sequence of the human AKAP10 gene or complement thereof;

(b) extending the nucleic acid primer using the target nucleic acid as a template; and

(c) determining the mass of the extended primer to identify the nucleotide present at a position corresponding to position 2073 or the complement thereof, thereby determining the presence or absence of an allelic variant. (emphasis added)

Claim 22 is directed to detecting the presence or absence of an allelic variant of a human AKAP10 gene by determining the identity of the nucleotide present at a position corresponding to position 2073 by determining the mass of the extended primer, which hybridizes to a position adjacent to position 2073. None of claims 21-37 include as subject matter determining the identity of the nucleotide at a position adjacent to a position corresponding to position 2073. Thus, the Restriction Requirement between Groups II and III is improper and should be withdrawn.

Claim 75

Applicant respectfully submits that claim 75, restricted into Groups XXIII-XXVI, is incorrectly restricted from Group I. Claim 75 recites:

> 75. A primer consisting essentially of nucleotide sequences selected from the group consisting of SEQ ID NO: 8, SEQ ID NO: 15, SEQ ID NO: 19 and SEQ ID NO: 20.

The specification teaches on page 17, line 21 through page 21, line 3:

> a first primer or probe that specifically hybridizes adjacent to or at a polymorphic region spanning a position corresponding to position 2073 of SEQ ID NO 1 or 3 of an AKAP10 allele or the complement thereof and a second primer or probe that specifically hybridizes adjacent to or at a polymorphic region spanning a position corresponding to positions selected from the group consisting of position 83587 of SEQ ID NO 13 or 17, position 129600 of SEQ ID NO 14 or 17, and position 156,277 of SEQ ID NO 18 or 17 of an AKAP10 allele or the complement thereof. Primers include, but are not limited to, nucleic acids consisting essentially of the nucleotide sequence of SEQ ID NO: 8, SEQ ID NO: 15, SEQ ID NO: 19 and SEQ ID NO 20.

Group I includes claims directed to primers or probes that hybridize adjacent to or at a polymorphic region spanning a polymorphic AKAP10 allele. For example, claim 11 recites:

> 11. A primer, probe or antisense nucleic acid molecule, comprising a sequence of nucleotides that specifically hybridizes adjacent to or at a polymorphic region spanning a position corresponding to position 2073 of SEQ ID No. 1 or 3 of an AKAP10 allele or the complement thereof.

Thus, the subject matter of claim 75, currently restricted to Groups XXIII through XXVI, is related to the subject matter of claim 11, currently restricted to Group I. In order for restriction to be proper, under 37 C.F.R. §§1.141 and 1.142, the restricted subject matter must be independent or distinct and there must be a burden on the Office to examine the claims in the same application. It is respectfully submitted that in this instance, the claimed "inventions" are not independent. The subject matter of both claim 11 and claim 75 is directed to probes comprising a sequence of nucleotides that specifically hybridizes adjacent to or at a polymorphic region spanning an AKAP10 allele or the complement thereof, with claim 75 reciting the specific sequences claimed. Further, there is no burden on the Office to examine the claimed subject matter in a single case. The primers and probes are classified in class 536, and the searches are, if not identical, substantially the same. Thus, claim 75 has been improperly restricted from Group I.

COMBINATION/SUBCOMBINATION

If the Restriction Requirement is maintained, applicant respectfully submits that the restriction requirement as between Groups I and VII-IX, Groups I and XI, and Groups I and XVI-XVIII is improper.

Groups I and VII-IX

Applicant respectfully urges that restriction between Groups I and VII-IX is improper. Group I includes claims directed to primers or probes that hybridize adjacent to or at a polymorphic region spanning a polymorphic AKAP10 allele. For example, claim 11 recites:

> 11. A primer, probe or antisense nucleic acid molecule, comprising a sequence of nucleotides that specifically hybridizes adjacent to or at a polymorphic region spanning a position corresponding to position 2073 of SEQ ID No. 1 or 3 of an AKAP10 allele or the complement thereof.

Groups VII through IX are directed to kits including the primer of claim 11. For example, claim 47 recites:

> 47. A kit for indicating whether a human subject has an increased susceptibility to morbidity or a predisposition for premature or increased or early mortality, comprising:
> a first primer or probe of claim 11; and
> a second primer or probe that specifically hybridizes adjacent to or at a polymorphic region spanning a position corresponding to positions selected from the group consisting of position 83587 of SEQ ID NO 13 or 17, position 129,600 of SEQ ID NO 14 or 17, and position 156,277 of SEQ ID NO 18 or 17 of an AKAP10 allele or the complement thereof.

Thus, Group I and Groups VII through IX are related as a combination (kits containing the primer or probe of claim 11) and a subcombination (the primer or probe of claim 11). Inventions that are related as a combination and subcombination are distinct and restriction may be proper **only if** it can be shown that the combination as claimed does not require the particulars of the subcombination as claimed for patentability **and** that the subcombination has utility by itself or in other combinations. See MPEP 808.05(c).

As between subject matter related as combination/subcombination, **two-way** distinctness is required, which applicant respectfully urges is absent in this instance. In this case, the combination (the kits of Groups VII-IX) requires the particulars of the subcombination (the primer or probe of Group I) for patentability. Therefore, as between Group I and Groups VII-IX, restriction is **not** proper. Since such restriction is improper, reconsideration and withdrawal of the restriction requirement as between Group I and Groups VII-IX is respectfully requested.

Groups I and XI

Applicant respectfully traverses the Restriction Requirement as between Groups I and XI. Applicant respectfully urges that restriction between Groups I and VII-IX is improper. Group I includes claims directed to nucleic acid that encodes a human AKAP10 variant protein. For example, claim 1 recites:

> 1. An isolated nucleic acid molecule, comprising a sequence of nucleotides that encodes a polypeptide as set forth in SEQ ID No. 2, except that the Ile residue at position 646 of SEQ ID NO: 2 is replaced with Val, Leu or Phe.

Group XI includes claims directed to transgenic animals that include a nucleic acid encoding a human AKAP10 variant protein or portion thereof which retains biological activity. For example, claim 55 recites:

> 55. A transgenic animal, comprising heterologous nucleic acid encoding a human AKAP10 variant protein or portion thereof which retains a biological activity exhibited by the full length variant protein, wherein the AKAP10 protein or portion thereof comprises valine at a position corresponding to amino acid residue position 646 of SEQ ID NO: 2, wherein:
> the transgenic nucleotide acid is expressed; and,
> as a result of the expression, the transgenic animal has an alteration in cellular signal transduction.

Thus, the claims of Groups I and XI are related as a combination (animals containing the human AKAP10 variant gene) and a subcombination (the human AKAP10 variant gene). As between subject matter related as combination/ subcombination, **two-way** distinctness is required (see MPEP 808.05(c)). Inventions that are related as a combination and subcombination are distinct and restriction may be proper **only if** it can be shown that the combination as claimed does not require the particulars of the subcombination as claimed for patentability **and** that the subcombination has utility by itself or in other combinations. Applicant respectfully urges that **two-way** distinctness is absent in this instance. The instant specification teaches that methods for making transgenic animals using a variety of trans-genes is well known in the art (page

71, lines 1-10). Therefore, patentability of the combination, the transgenic animal of Group XI, requires the particulars of the subcombination, the group I human AKAP10 variant gene, for patentability. Therefore, as between Group I and Group XI restriction is **not** proper.

Groups I and XVI-XVIII

Applicant respectfully traverses the Restriction Requirement as between Group I and Groups XVI-XVIII. Group I includes claims directed to nucleic acid that encodes a human AKAP10 variant protein. For example, claim 3 recites:

> 3. An isolated nucleic acid molecule of claim 1, comprising the sequence of nucleotides set forth as position 138 to position 2126 of SEQ ID NO: 1, except that the nucleotide at position 2073 of SEQ ID NO: 1 is replaced with a nucleotide selected from the group consisting of G, T and C.

Groups XVI-XVIII includes claims directed to solid supports that includes a polymorphic region of an AKAP10 gene. For example, claim 69 recites:

> 69. A solid support comprising a nucleic acid comprising a polymorphic region of an AKAP10 gene, wherein the polymorphic region comprises a nucleotide at a position corresponding to position 2073 of SEQ ID NO: 1 that is other than an A or other than T on the complementary strand.

Thus, the claims of Group I and the claims of Groups XVI-XVIII are related as a combination (solid supports containing the human AKAP10 variant gene) and a subcombination (the human AKAP10 variant gene). As between subject matter related as combination/subcombination, **two-way** distinctness is required. As discussed above, inventions that are related as a combination and subcombination are distinct and restriction may be proper **only if** it can be shown that the combination as claimed does not require the particulars of the subcombination as claimed for patentability. Applicant respectfully urges that **two-way** distinctness is absent in this instance. The instant specification teaches that methods for making solid supports that include nucleic acid molecules, and arrays of such probes, is well known in the art (for example, see

Cronin *et al.* (1996) Human Mutation 7:244, Kozal *et al.* (1996) Nature Medicine 2:753, and U.S. Patent 6,156,501, cited on pages 47-48 of the specification). Therefore, patentability of the combination, the solid supports of Groups XVI-XVIII, requires the particulars of the subcombination, the Group I human AKAP10 variant gene, for patentability. Therefore, as between Group I and Groups XVI-XVIII restriction is **not** proper.

In light of the above, applicant respectfully requests that, if the restriction requirement is maintained, the subject matter currently restricted to Restriction Groups I, VII through IX, XI, XVI through XVIII, and XXIII through XXVI be combined into Group I. Group I would be directed to the subject matter of claims 1-20, 44-50, 55, 56, 69-71, and 75.

Multiple Patents

The applicant is entitled to have more than one claim per application examined; in this instance there are 75 claims and a 26-way restriction requirement. Applicant is entitled to claim the subject matter under one or more claims of varying scope. Under U.S. patent practice, an applicant is not required to claim each and every embodiment of the subject matter they wish to protect as separate single claimed embodiments and in different patents. Thus, this restriction is improper.

If the requirement is maintained, the Office is reminded that the applicant ultimately could be granted multiple patents, each of which would include claims to overlapping subject matter, that expire on different dates. Despite the overlapping subject matter, the later issuing patents could not be held to constitute obviousness-type double patenting over the earlier issuing patent. See MPEP 806, paragraph 3, which states:

> [w]here inventions are related as disclosed but are not distinct as claimed, restriction is never proper. Where restriction is required by the Office double patenting cannot be held, and thus, it is imperative the requirement should never be made where related inventions as claimed are not distinct.

See, also MPEP 804.01, which states:

> 35 U.S.C. 121 authorizes the Commissioner to restrict the claims in a patent application to a single invention when independent and distinct inventions are presented for examination. The third sentence of 35 U.S.C. 121 prohibits the use of a patent issuing on an application with respect to which a requirement for restriction has been made, or on an application filed as a result of such a requirement, as a reference against any divisional application, if the divisional application is filed before the issuance of the patent. The 35 U.S.C. 121 prohibition applies only where the Office has made a requirement for restriction. The prohibition does not apply where the divisional application was voluntarily filed by the applicant and not in response to an Office requirement for restriction. This apparent nullification of double patenting as a ground of rejection or invalidity in such cases imposes a heavy burden on the Office to guard against erroneous requirements for restrictions where the claims define essentially the same invention in different language and which, if acquiesced in, might result in the issuance of several patents for the same invention.

For example, if the restriction of the subject matter in Group I and Group XI is maintained, applicant ultimately could be granted two patents, one directed to the animal containing the human AKAP10 variant gene, and the other to the human AKAP10 variant gene. The patents are not required to be co-owned, and they could expire on different dates. Thus, for example, if the claims to the combination, the transgenic animals containing the human AKAP10 variant gene, issued first, then a patent encompassing the subcombination, the human AKAP10 variant gene, issued later could not be held to constitute obvious-type double patenting over the earlier issuing patent.

Similarly, if the claims are divided as in the restriction requirement for Groups XVI-XVIII, applicant ultimately could be granted four patents, one to the human AKAP10 variant gene, and three to solid supports containing the human AKAP10 variant gene (since the Office has restricted the subject matter of claims 69-71 into three groups by restriction to a single nucleotide sequence). None of the patents are required to be co-owned and all could expire on different dates. Thus, for example, if the claims to the combination, the solid

supports containing the human AKAP10 variant gene, issued first, then a patent encompassing the subcombination, the human AKAP10 variant gene, issued later could not be held to constitute obvious-type double patenting over the earlier issuing patent. Applicant respectfully submits that the instantly claimed subject matter does not warrant multiple patents, and certainly not twenty-six patents. Thus, the Restriction Requirement as currently drafted is improper.

* * *

In view of the provisional election, amendments and remarks herein, examination on the merits is respectfully requested.

Respectfully submitted,
HELLER EHRMAN WHITE & MCAULIFFE LLP

By: _____
Stephanie Seidman
Registration No. 33,779

Attorney Docket No. 24736-2035
Address all correspondence to:
Stephanie L. Seidman, Esq.
HELLER EHRMAN WHITE & MCAULIFFE LLP
4350 La Jolla Village Drive, 7th Floor
San Diego, CA 92122-1246
Telephone: 858 450-8400
Facsimile: 858 587-5360
e-mail: sseidman@HEWM.com

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: BRAUN

Serial No.: 09/834,700

Confirmation No.: 5035

Filed: April 12, 2001

For: *POLYMORPHIC KINASE ANCHOR PROTEINS AND NUCLEIC ACIDS ENCODING THE SAME*

Art Unit: 1632

Examiner: Li, Q. J.

CERTIFICATE OF MAILING BY "EXPRESS MAIL"

"Express Mail" Mailing Label No.: **EV 175674600 US**
Date of Deposit: November 20, 2002

I hereby certify that this paper and the attached papers are being deposited with the United States Postal "Express Mail Post Office to Addressee" Service under 37 CFR §1.10 on the date indicated above and addressed to:

Commissioner for Patents
U.S. Patent and Trademark Office
P. O. Box 2327
Arlington, VA 22202

Michael Lough

ATTACHMENT TO THE AMENDMENT SHOWING MARKED-UP PARAGRAPHS AND CLAIMS IN ACCORDANCE WITH (37 CFR §1.121)

IN THE SPECIFICATION:

Amend the paragraph at page 22, lines 12-13, as follows:

Microarrays [Micrarrays] are well known (see, *e.g.*, U.S. Patent Nos. 5,837,832; 5,858,659; 6,043,136; 6,043,031 and 6,156,501).

Amend the paragraph at page 40, line 29 through page 41, line 22, as follows:

Polymorphisms of the genome can lead to altered gene function, protein function or mRNA instability. AKAPs provide a mechanism for regulating ubiquitous cAMP-dependent kinase (PKA) activity by tethering PKA to specific subcellular locations thereby segregating it with particular components in a given signaling pathway and contributing to specificity in cellular responses to extracellular signals. AKAPs thus play a fundamental role in the basic functioning of cells, the response of cells to their environment and ultimately in the coordination of vital systems within an organism. Therefore, polymorphisms in AKAP gene sequences may significantly affect the proper functioning of cells and systems within organisms and could be directly linked with certain disorders or could predispose an organism to a variety of diseases and disorders, especially those involving alterations in cellular protein phosphorylation and/or signal transduction. Among such disorders and diseases are: neurodegenerative [neurodegeneratives] diseases, such as Alzheimer's Disease, cardiovascular disorders, cardiac disorders, particularly disorders associated with altered left

ventricular function, cardiomyopathies, proliferative disorders, bipolar disorder and other neurological disorders, obesity, diabetes and certain peripheral retinopathies, such as retinitis pigmentosa. The discovery of AKAP gene polymorphisms, such as those described herein, provides for the identification and development of diagnostic and prognostic methods, also provided herein, and the development of drug therapies and treatment regimens. Furthermore, polymorphisms of AKAP genes aid in the study of AKAP protein structure and function, which also contributes to the development of diagnostic methods and therapies.

Amend the Table at page 43, lines 26-29 as follows:

Name	GenBank Accession [Acession] No.	SNP	Location
10-1	AC005730	T/C	156277
10-6	AC005730	C/G	83587
10-7	AC005730	G/A	129600

Amend the paragraph at page 69, lines 14-25 as follows:

An example of possible candidate morbidity susceptibility genes are mutants of the A kinase anchoring protein (AKAP) genes. Protein phosphorylation is an important mechanism for enzyme regulation and signal transduction in eukaryotic cells. cAMP dependent protein kinase [kinsae] (PKA) mediates a variety of hormonal and neurotransmitter responses by phosphorylating [phospyhorylating] a wide variety of substrates including enzymes, membrane receptors, ion channels and transcription factors. AKAPs direct the subcellular localization of cAMP-dependent protein kinase by binding to its regulatory subunits and therefore plays a role in G-protein mediated receptor-signalling pathways. (Huang et al. Proc. Natl. Acad. Sci., USA 94:11184, 1997). AKAPs have a PKA binding region located in their COOH-terminal portion.

Amend the paragraph at page 91, line 23 through page 92, line 21 as follows:

Ribozymes may be prepared by chemical synthesis or produced by recombinant vectors according to methods established for the synthesis of RNA molecules. See, e.g., Sambrook et al., Molecular Cloning, A Laboratory Manual, 2d ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989), incorporated herein by reference. The ribozyme sequence may be synthesized, for example, using RNA polymerases such as T7 or SP6. The ribozymes may be prepared from a corresponding DNA sequence (DNA which on transcription yields a ribozyme) operably linked to an RNA polymerase promoter such as the promoter for T7 RNA polymerase or SP6 RNA polymerase. A DNA sequence corresponding to a ribozyme may be ligated in to a DNA vector, such as a plasmid, bacteriophage or other virus. Where the transfer vector contains an RNA polymerase promoter operably linked to DNA corresponding to a ribozyme, the ribozyme may be conveniently produced upon incubation with an RNA polymerase. Ribozymes may therefore be produced in vitro by incubation of RNA polymerase with an RNA polymerase promoter operably linked to DNA corresponding to a ribozyme, in the presence of ribonucleotides. In vivo, prokaryotic [procaryotic] or eukaryotic [eucaryotic] cells (including mammalian cells) may be transfected with an appropriate vector containing genetic material corresponding to a ribozyme, operably linked to an RNA polymerase promoter such that the ribozyme is transcribed in the host cell. Ribozymes may be directly transcribed in vivo from a transfer vector, or alternatively, may be transcribed as part of a larger RNA molecule. For example, DNA corresponding to ribozyme sequence may be ligated into the 3′ end of a carrier gene, for example, after a translation stop signal. Larger RNA molecules may help to stabilize the ribozyme molecules against nuclease digestion within the cells. On translation the carrier gene may give rise to a protein, whose presence can be directly assayed if desired, for example, by enzymatic reaction when the carrier gene encodes an enzyme.

Amend the paragraph at page 94, lines 8-31 as follows:

The following examples are included for illustrative purposes only and are not intended to limit the scope of the invention. The practice of methods and development of the products provided herein employ, unless otherwise indicated, conventional techniques of cell biology, cell culture, molecular biology, transgenic biology, microbiology, recombinant DNA, and immunology, which are within the skill of the art. Such techniques are explained fully in the literature. See, for example, Molecular Cloning A Laboratory Manual, 2nd Ed., ed. by Sambrook, Fritsch and Maniatis (Cold Spring Harbor Laboratory Press: 1989); DNA Cloning, Volumes I and II (D.N. Glover ed., 1985); Oligonucleotide Synthesis (M.J. Gait ed., 1984); Mullis *et al.* U.S. Patent No. 4,683,195; Nucleic Acid Hybridization [Hybridizatiion] (B.D. Hames & S.J. Higgins eds. 1984); Transcription and Translation (B.D. Hames & S.J. Higgins eds. 1984); Culture of Animal Cells (R.I. Freshney, Alan R. Liss, Inc., 1987); Immobilized Cells and Enzymes (IRL Press, 1986); B. Perbal, A Practical Guide To Molecular Cloning (1984); the treatise, Methods In Enzymology (Academic Press, Inc., New York); Gene Transfer Vectors For Mammalian Cells (J.H. Miller and M.P. Calos eds., 1987, Cold Spring Harbor Laboratory); Methods In Enzymology, Vols. 154 and 155 (Wu *et al.* eds., Immunochemical Methods In Cell and Molecular Biology (Mayer and Walker, eds., Academic Press, London, 1987); Handbook of Experimental Immunology, Volumes I-IV (D.M. Weir and C.C. Blackwell, eds., 1986); Manipulating the Mouse Embryo, (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986).

Amend the paragraph at page 101, line 28 through page 102, line 2 as follows:

Thermal [Themal] cycling was performed in 0.2 mL tubes or 96 well plate using an MJ Research Thermal Cycler (Waltham, MA) (calculated temperature) with the following cycling parameters: 94°C for 5 min; 45 cycles: 94°C for 20 sec, 56°C for 30 sec; 72°C for 60 sec; 72°C 3 min.

IN THE CLAIMS:

Please amend claim 3 as follows (insertions are underlined, deletions are [bracketed]):

3. (Amended) An isolated nucleic acid molecule of claim 1, comprising the sequence of nucleotides [nucletides] set forth as position 138 to position 2126 of SEQ ID NO: 1, except that the nucleotide at position 2073 of SEQ ID NO: 1 is replaced with a nucleotide selected from the group consisting of G, T and C.